

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
2 March 2000 (02.03.2000)

PCT

(10) International Publication Number  
**WO 00/10588 A3**

(51) International Patent Classification<sup>7</sup>: A61K 31/00, 38/00, A61P 11/00, 11/06

(21) International Application Number: PCT/US99/18696

(22) International Filing Date: 17 August 1999 (17.08.1999)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:  
60/097,023 18 August 1998 (18.08.1998) US

(71) Applicant (for all designated States except US): THE REGENTS OF THE UNIVERSITY OF CALIFORNIA [US/US]; 12th Floor, 1111 Franklin Street, Oakland, CA 94607-5200 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): NADEL, Jay, A. [US/US]; 2373 Pacific Avenue, San Francisco, CA 94115 (US). TAKEYAMA, Kiyoshi [JP/JP]; 4-6-1-108, Seta, Setagaya-ku, Tokyo 158 (JP).

(74) Agent: SHERWOOD, Pamela, J.; Bozicevic, Field & Francis LLP, 200 Middlefield Road, Suite 200, Menlo Park, CA 94025 (US).

(81) Designated States (national): AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

— With international search report.

(88) Date of publication of the international search report:  
25 May 2001

(15) Information about Correction:

Previous Correction:

see PCT Gazette No. 32/2000 of 10 August 2000, Section II

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

DOCKETED

(54) Title: EPIDERMAL GROWTH FACTOR RECEPTOR ANTAGONISTS FOR TREATING HYPERSECRETION OF MUCUS IN THE LUNGS

(57) Abstract: Hypersecretion of mucus in the lungs is inhibited by the administration of an epidermal growth factor receptor (EGF-R) antagonist. The EGF-R antagonist may be in the form of a small organic molecule, an antibody, or portion of an antibody that binds to and blocks the EGF receptor. The EGF-R antagonist is preferably administered by injection in an amount sufficient to inhibit formation of goblet cells in pulmonary airways. The degranulation of goblet cells that results in airway mucus production is thereby inhibited. Assays for screening candidate agents that inhibit goblet cell proliferation are also provided.

Document AA  
Cited in IDS for UCSF085CIP  
Serial No. 09/616,223  
filed July 14, 2000

WO 00/10588 A3

# INTERNATIONAL SEARCH REPORT

Internati      Application No  
PCT/US 99/18696

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7    A61K31/00    A61K38/00    A61P11/00    A61P11/06

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7    A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
T	<p>TAKEYAMA, K. ET AL: "Oxidative stress causes mucin synthesis via transactivation of epidermal growth factor receptor: role of neutrophils"</p> <p>JOURNAL OF IMMUNOLOGY, vol. 164, no. 3, 1 February 2000 (2000-02-01), pages 1546-1552, XP000906999 the whole document</p> <p style="text-align: center;">--- -/--</p>	<p>1-16, 20-27</p>

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents:

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*S\* document member of the same patent family

Date of the actual completion of the international search

13 December 2000

Date of mailing of the international search report

05 01 01

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl.  
Fax: (+31-70) 340-3016

Authorized officer

Mair, J

# INTERNATIONAL SEARCH REPORT

Internati Application No

PCT/US 99/18696

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	TAKEYAMA, K. ET AL: "Epidermal growth factor system regulates mucin production in airways" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES USA, vol. 96, no. 6, 16 March 1999 (1999-03-16), pages 3081-3086, XP000906985	1-14, 20-27
P,A	the whole document	15-19
P,X	WO 99 32121 A (SMITHKLINE BEECHAM CORPORATION) 1 July 1999 (1999-07-01)  page 40, line 25 page 30, line 32	1,2, 8-10, 20-23
X	WO 97 19065 A (CELLTECH THERAPEUTICS LIMITED) 29 May 1997 (1997-05-29)  page 14, line 25 page 15, line 2 page 15, line 10-12	1,2, 8-10,12, 20-23
X	GRANDIS, J.R. ET AL: "Inhibition of epidermal growth factor receptor gene expression and function decreases proliferation of head and neck squamous carcinoma but not normal mucosal epithelial cells" ONCOGENE, vol. 15, no. 4, 24 July 1997 (1997-07-24), pages 409-416, XP000910341	20-22, 24-27
A	the whole document especially page 415, lefthand column, third paragraph and righthand column, second and third paragraphs	15,16
X	KUMAR, R.K. ET AL: "Cooperative interaction of autocrine and paracrine mitogens for airway epithelial cells" CELL BIOLOGY AND TOXICOLOGY, vol. 14, no. 4, August 1998 (1998-08), pages 293-299, XP000909220 the whole document	15,16, 20-22

-/--

# INTERNATIONAL SEARCH REPORT

Internati      Application No  
PCT/US 99/18696

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>GUZMAN, K. ET AL: "Epidermal growth factor regulates expression of the mucous phenotype of rat tracheal epithelial cells"</p> <p>BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, vol. 217, no. 2, 14 December 1995 (1995-12-14), pages 412-418, XP000907100 the whole document especially page 417, last paragraph</p> <p style="text-align: center;">---</p>	1-16
A	<p>AMISHIMA, M. ET AL: "Expression of epidermal growth factor and epidermal growth factor receptor immunoreactivity in the asthmatic human airway"</p> <p>AMERICAN JOURNAL OF RESPIRATORY AND CRITICAL CARE MEDICINE, vol. 157, no. 6, June 1998 (1998-06), pages 1907-1912, XP000910438 the whole document</p> <p style="text-align: center;">---</p>	1-14
A	<p>STRAWN AND SHAWVER: "Tyrosine kinases in disease: overview of kinase inhibitors as therapeutic agents and current drugs in clinical trials"</p> <p>EXPERT OPINION ON INVESTIGATIONAL DRUGS, vol. 7, no. 4, April 1998 (1998-04), pages 553-573, XP000893015 cited in the application page 557, left-hand column -page 565, left-hand column</p> <p style="text-align: center;">---</p>	1-14, 20-27
A	<p>NYCE, J.W. ET AL: "DNA antisense therapy for asthma in an animal model"</p> <p>NATURE, vol. 385, 20 February 1997 (1997-02-20), pages 721-725, XP000891493 cited in the application the whole document</p> <p style="text-align: center;">---</p>	1-14, 20-27
A	<p>KAWAMOTO, T. ET AL: "Growth stimulation of A431 cells by epidermal growth factor: Identification of high-affinity receptors for epidermal growth factor by an anti-receptor monoclonal antibody"</p> <p>PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES USA, vol. 80, March 1983 (1983-03), pages 1337-1341, XP000891494 cited in the application</p> <p style="text-align: center;">---</p>	1-14, 20-27
X	<p>the whole document</p> <p style="text-align: center;">---</p>	15,16

-/--

## INTERNATIONAL SEARCH REPORT

Internati Application No

PCT/US 99/18696

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	SCHMIDT, M. ET AL: "Targeted inhibition of tumour cell growth by a bispecific single-chain toxin containing an antibody domain and TGF.alpha" BRITISH JOURNAL OF CANCER, vol. 74, no. 6, 1996, pages 853-862, XP000893031 cited in the application the whole document	1-14, 20-27
A	LORIMER, I.A. ET AL: "Immunotoxins that target an oncogenic mutant epidermal growth factor receptor expressed in human tumors" CLINICAL CANCER RESEARCH, vol. 1, 1995, pages 859-864, XP000891452 cited in the application the whole document	1-14, 20-27
A	GOLDSTEIN, N.I. ET AL: "Biological efficacy of a chimeric antibody to the epidermal growth factor receptor in a human tumor xenograft model" CLINICAL CANCER RESEARCH, vol. 1, 1995, pages 1311-1318, XP000891451 cited in the application the whole document	1-14, 20-27
A	WO 90 03374 A (THE UPJOHN COMPANY) 5 April 1990 (1990-04-05) page 34; claim 11	1-14
A	EP 0 157 284 A (CAMILLO CORVI S.P.A.) 9 October 1985 (1985-10-09) abstract	1-14
A	LOU, Y.-P. ET AL: "Platelet-activating factor induces goblet cell hyperplasia and mucin gene expression in airways" RESPIRATORY AND CRITICAL CARE MEDICINE, vol. 157, no. 6, June 1998 (1998-06), pages 1927-1934, XP000974347 cited in the application the whole document	17-19
A	SAUMA, S. ET AL: "Colon goblet cells lose proliferative response to TGFalpha as they differentiate" INTERNATIONAL JOURNAL OF CANCER, vol. 61, no. 6, 1995, pages 848-853, XP000972763 the whole document	15

-/--

# INTERNATIONAL SEARCH REPORT

Internati	Application No.
PCT/US 99/18696	

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>BLYTH, D.I. ET AL: "Induction, duration and resolution of airway goblet cell hyperplasia in a murine model of atopic asthma: effect of concurrent infection with respiratory syncytial virus and response to dexamethasone"</p> <p>AMERICAN JOURNAL OF RESPIRATORY CELL AND MOLECULAR BIOLOGY, vol. 19, no. 1, July 1998 (1998-07), pages 38-54, XP000974408 the whole document</p>	17-19
A	<p>LUNDGREN, J.D. ET AL: "Dexamethasone reduces rat tracheal goblet cell hyperplasia produced by human neutrophil products"</p> <p>EXPERIMENTAL LUNG RESEARCH, vol. 14, no. 6, 1998, pages 853-863, XP000974414 the whole document</p>	17-19
A	<p>CRESSMAN, V.L. ET AL: "The relationship of chronic mucin secretion to airway disease in normal and CFTR-deficient mice"</p> <p>AMERICAN JOURNAL OF RESPIRATORY CELL AND MOLECULAR BIOLOGY, vol. 19, no. 6, 1998, pages 853-866, XP000974409 the whole document</p>	17-19

# INTERNATIONAL SEARCH REPORT

Inte. onal application No.  
PCT/US 99/18696

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
  
Although claims 1-14 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compositions.
2. ☒ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  
  
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☒ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-14, 20-27

Pharmaceutical formulations containing an epidermal growth factor receptor antagonist and their use in relation to the treatment of hypersecretion of mucus in the lungs.

2. Claim : 15 and 16

An in vitro method for screening candidate agents for decreasing goblet cell proliferation.

3. Claims: 17-19

An in vivo method for screening candidate agents for inhibiting goblet cell proliferation or mucus secretion.



## FURTHER INFORMATION CONTINUED FROM PCT/SA/ 210

## Continuation of Box I.2

Present claims 1, 2, 4-14 and 20-27 relate to a compound defined by reference to a desirable characteristic or property, namely "an epidermal growth factor receptor (EGF-R) antagonist" etcetera. The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT for a limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compound specifically mentioned in claim 3 and those for which experimental data is given with due regard to the general idea underlying the application.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 99/18696

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9932121 A	01-07-1999	AU 1924699 A EP 1037639 A ZA 9811631 A	12-07-1999 27-09-2000 21-06-1999
WO 9719065 A	29-05-1997	AU 7631496 A EP 0862560 A US 5958935 A	11-06-1997 09-09-1998 28-09-1999
WO 9003374 A	05-04-1990	AU 4203789 A	18-04-1990
EP 157284 A	09-10-1985	IT 1173549 B AT 45357 T DE 3572171 D JP 60224690 A KR 9104428 B US 4652568 A	24-06-1987 15-08-1989 14-09-1989 09-11-1985 27-06-1991 24-03-1987